

# Left Ventricular Support by Catheter-Mounted Axial Flow Pump Reduces Infarct Size

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| <b>OBJECTIVES</b>  | We sought to investigate the effect of a catheter-mounted microaxial blood pump (Impella, Aachen, Germany) on myocardial infarct size.   |
| <b>BACKGROUND</b>  | The small rotary blood pump Impella provides unloading of the left ventricle and is introducible via the femoral artery.   |
| <b>METHODS</b>     | Myocardial infarction was induced by occlusion of major branches of the left anterior descending coronary artery for 60 min followed by 120 min of reperfusion in 26 sheep. The animals were allocated to four groups: group 1 had no support; group 2 was fully supported with the pump during ischemia and reperfusion; group 3 was supported during reperfusion only; and group 4 was partially supported during reperfusion. Infarct size, hemodynamics, myocardial oxygen consumption, lactate extraction, and myocardial flow were analyzed.   |
| <b>RESULTS</b>     | Infarct size was significantly reduced in the pump-supported animals (percent area at risk in group 1: $67.2 \pm 4.6\%$ ; group 2: $18.1 \pm 10\%$ ; group 3: $41.6 \pm 5.8\%$ ; group 4: $54 \pm 8\%$ ; $p = 0.00001$ ). The pump produced $4.1 \pm 0.1$ l/min at full support and $2.4 \pm 0.1$ l/min at partial support. The pump significantly increased the diastolic and mean blood pressures (groups 2, 3, and 4) and significantly decreased the left ventricular end-diastolic pressure (groups 2 and 3). During ischemia, myocardial flow was not influenced by pump support. At reperfusion, the fully supported group had significantly higher myocardial flow. Pump support reduced myocardial oxygen consumption significantly, and this reduction correlates strongly with the reduction in infarct size ( $r = 0.9$ ). |
| <b>CONCLUSIONS</b> | Support by a microaxial blood pump reduces myocardial oxygen consumption during ischemia and reperfusion and leads to a reduction of infarct size. This reduction in infarct size correlates with the degree of unloading during reperfusion. (J Am Coll Cardiol 2003;41:1087-95) © 2003 by the American College of Cardiology Foundation  |

The transvalvular assist device Impella (Aachen, Germany) is a potent, miniaturized pump that offers the possibility of unloading the left ventricle (LV) via the femoral placement (1). In vivo and clinical use of this device has indicated that the pump produces a mean flow of 4.2 l/min at maximal rotational speed (2).

Mechanical unloading of the myocardium during ischemia and reperfusion has been shown to reduce LV pressure work and myocardial oxygen consumption (3-5). However, the installation of a left heart bypass during myocardial infarction (MI) is a cumbersome clinical procedure, with important comorbidity.

Pharmacologic approaches, such as the early use of beta-blockers, nitroglycerin, and angiotensin-converting enzyme inhibitors, have achieved infarct size reduction in experimental models (6-10). The use of beta-blockers and angiotensin-converting enzyme inhibitors has rapidly advanced from experimental studies to the clinical recommendation as standard therapy in most patients experiencing an MI. However, clinical trials on the early use (first day of

infarction) showed an increased incidence of hypotension (9-12).

Mechanical support combines the beneficial effects of myocardial unloading and an increase in perfusion pressure. It can therefore be used early, even during ischemia and in myocardial failure.

This new pump allows unloading of the LV via a peripheral approach in the setting of acute MI. We wanted to investigate the effect of this microaxial blood pump on MI size.

## METHODS

Studies were carried out in 26 adult Dorset sheep weighing  $68.5 \pm 8.7$  kg. The study protocol was approved by the Ethical Committee for Laboratory Animals of the Catholic University of Leuven, and all experiments were performed according to the Committee's guidelines.

**The microaxial blood pump.** The Impella LV support system is a miniaturized rotary blood pump (diameter 6.4 mm). The pump incorporates a rotor driven by an electrical motor and has an inflow cannula (Fig. 1). The pump is placed through the aortic valve and aspirates blood from the LV cavity and expels it in the ascending aorta. The performance of this pump depends on the rotary speed (which is maximized at 32,000 rotations/min) and the pressure head which the pump has to face (1). In the clinical condition, this pressure head equals the aortic blood pres-

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#### Abbreviations and Acronyms

|     |                                 |
|-----|---------------------------------|
| BP  | = blood pressure                |
| CBF | = coronary blood flow           |
| Hb  | = hemoglobin                    |
| LER | = lactate extraction ratio      |
| LV  | = left ventricle/ventricular    |
| MI  | = myocardial infarction/infarct |
| RV  | = right ventricle/ventricular   |
| TTC | = triphenyltetrazolium chloride |

sure (BP) minus the LV pressure. A pressure sensor is located in front of the rotor and continuously registers this pressure difference. This pressure signal is an indicator of the correct position of the pump. The pump flow produced in physiologic conditions at maximal rotational speed is in the range of 4.2 to 4.6 l/min. The driving console of the pump allows the management of pump speed (by 9 gradations) and displays the pressure difference between inflow and outflow.

The pump is approved as safe for human use up to seven days. The pump is clinically used in the support of coronary artery bypass grafting and in postcardiotomy heart failure. The feasibility of this pump was tested in a randomized, multicenter trial in 200 patients (13). The inflammatory response in patients who had an operation with pump support was significantly reduced compared with the control

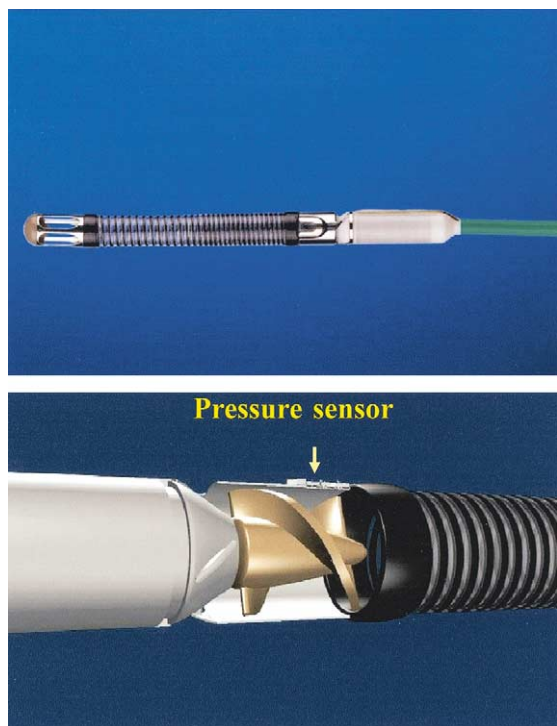
group, whose operation involved the heart-lung machine. Placement of the LV support system was uneventful, and no aortic insufficiency was shown with the pump in the transvalvular position.

**Surgical preparation.** Animals were premedicated with ketamine (15 mg/kg intramuscularly). General anesthesia was induced and maintained with 0.5% to 2.0% halothane. The animals were intubated and mechanically ventilated by an Engström II respirator (Datex Ohmeda, Stockholm, Sweden) with room air supplemented with oxygen to maintain arterial blood gasses in the physiologic range. Surface electrocardiographic (ECG) leads were applied, a gastric tube inserted, and a fluid-filled catheter placed in the left ear artery to enable monitoring of the vital parameters. A left thoracotomy was performed in the fourth intercostal space. The pericardium was opened, and the heart was suspended in a pericardial cradle. A 6-mm ultrasonic transit time flow probe was placed around the left main coronary artery (Transonic Inc., Ithaca, New York), and a 20-mm probe was placed around the pulmonary artery. A micromanometer-tipped catheter transducer (Millar Instruments, Inc., Houston, Texas) was placed in the LV cavity through the apex of the heart. Fluid-filled catheters were placed in the left atrium, jugular vein, and coronary sinus. The hemiazygos vein was ligated.

The micropump was inserted via the carotid artery (cut-down), and the entrance of the inflow cannula in the LV was checked by the differential pressure signal. Snares were placed around the two first diagonal branches of the left anterior descending coronary artery.

**Experimental protocol.** Baseline measurements included hemodynamic values (arterial BP, cardiac output, left atrial pressure, LV pressure, first derivative of LV pressure), coronary flow, arterial and coronary sinus blood gas analysis, and lactate sampling. Two major diagonal branches of the left anterior descending coronary artery were ligated for 1 h. Reperfusion was allowed for 2 h. Hemodynamic values and flow data were continuously recorded. Sampling for blood gasses and lactate content was done at baseline and at 5, 30, and 60 min of ischemia; at 5, 30, 60, and 120 min of reperfusion; and 5 min after the pump was stopped. Group 1 (n = 8) served as a control group, and no support was given. In group 2 (n = 6), the Impella pump was started at maximal rotational speed from the moment of ischemia until the completion of 2 h of reperfusion. In group 3 (n = 6), ventricular support was started at the moment of reperfusion. In group 4 (n = 6), ventricular support was again started at reperfusion, but only half of the baseline cardiac output was provided by the pump (so-called "partial support").

**Myocardial oxygen consumption.** The left coronary artery in sheep exclusively supplies the entire LV, with minimal overlap to the right ventricle (RV) (14,15). All venous blood from the LV drains into the coronary sinus, whereas venous blood from the RV does not drain into the coronary sinus, but goes directly to the right atrium (16). Thus, measure-



**Figure 1.** The microaxial blood pump has an outer diameter of 6.4 mm and is driven by a miniaturized electrical motor incorporated in the housing. The cannula (upper panel) is placed across the aortic valve, and the pump aspirates the blood from the left ventricular cavity to expel it in the ascending aorta. A differential pressure sensor (lower panel) continuously measures the pressure difference between the inflow and outflow of the pump and allows the calculation of the produced pump flow.

ment of the left main coronary blood flow (CBF) represents total blood flow to the LV, and the arterio-coronary sinus oxygen content difference reflects the amount of oxygen utilized by the LV. For determination of myocardial oxygen consumption, aortic and coronary sinus blood samples were drawn simultaneously into heparinized syringes. The hemoglobin (Hb) concentration, oxygen partial pressure ( $P_{O_2}$ ), and blood saturation ( $Sa_{O_2}$ ) were immediately analyzed with an automatic blood gas, oximetry, electrolyte, and metabolite analyzer (ABL System 625 Radiometer Medical A/S, Copenhagen, Denmark).

Left ventricular myocardial oxygen consumption ( $MVO_2$ ) was normalized to LV weight and expressed in ml/min per 100 g of LV mass. It was defined as a product of mean left main CBF, and the difference in oxygen content between arterial ( $aO_2$ ) and coronary sinus ( $VO_2$ ) blood was expressed in ml  $O_2$ /dl of blood:

$$MVO_2 = (aO_2 - VO_2) \times CBF$$

The oxygen content in arterial and venous blood was calculated as a sum of oxygen transported by Hb and oxygen dissolved in blood plasma. The oxygen transported by sheep Hb equals  $1.35 \times \text{Hb concentration (g/dl)} \times \text{blood saturation}$  (17). Oxygen dissolved in plasma was calculated as oxygen partial pressure (mm Hg)  $\times 0.0031$  (oxygen solubility coefficient in blood plasma at 37°C) (18). Oxygen content in blood was expressed in ml  $O_2$ /dl of blood:

$$aO_2 (VO_2) = (1.35 \times \text{Hb} \times sO_2/100\%) + (pO_2 \times 0.0031)$$

**Lactate metabolism.** The balance between aerobic and anaerobic myocardial metabolism was studied based on lactate metabolism (19). The arterial blood lactate concentration and coronary sinus lactate concentration were measured with an automatic blood gas, oximetry, electrolyte, and metabolite analyzer (ABL System 625).

The lactate extraction ratio (LER), expressed as percentage, represents the amount of lactate that is extracted by the LV from arterial blood. It is calculated by dividing the arterio-coronary sinus lactate concentration difference by the lactate concentration in arterial blood:

$$LER = (AL - VL) \times 100\%/AL$$

where AL is arterial lactate and VL is venous lactate.

Positive values indicate lactate uptake, and negative values represent lactate released into coronary sinus blood.

**MI size determination.** Upon termination of the experiment, the hearts were arrested by potassium chloride. The snares around the target coronary arteries were re-occluded. The aorta was cross-clamped, and a catheter was inserted into the aortic root. First, 500 ml of saline solution and then 500 ml of Evans' blue dye were administered by a continuous infusion at a perfusion pressure of 100 mm Hg. The right and left atria were opened to allow free drainage of blood and stain. The hearts were removed and cut in 1-cm-thick slices perpendicular to the long axis, and the slices were placed in a bath of 1% triphenyltetrazolium

chloride (TTC) at 37°C during 5 min to allow staining of the infarct-related areas.

After staining, the RV, both atria, and the valvular apparatus were excised. The complete heart, LV, and each LV slice were weighed separately. Both surfaces of each slice were photographed. Measurement of the area at risk and infarct size was performed by computer-assisted planimetry. The weights of measured areas was analyzed: the area at risk was expressed as the percent of LV mass, and infarct size was expressed as the percent of area at risk (20).

**Myocardial blood flow.** Myocardial flow was analyzed with the colored microspheres technique (21). At baseline, at 30 min of ischemia, at 60 min of reperfusion, and at 5 min after the pump was stopped, a set of 9 million of 15  $\mu\text{m}$  colored polystyrene microspheres (Triton Technology, Inc., San Diego, California) was injected through a left atrial catheter. Arterial reference blood was withdrawn over 90 s from the aorta at a flow rate of 10 ml/min. Upon termination of the experiment, 1-g tissue samples were isolated from the different regions of the myocardium. Subendocardial and subepicardial samples were taken from the area at risk and from the lateral wall (control area). The microspheres were recovered from the tissue samples by digestion of the tissue by KOH. Subsequently, the samples were filtered, dye-extracted, and examined by spectrophotometry.

**Data analysis.** All pressure transducers were connected to a Triton pressure module. The hemodynamic and ECG parameters were recorded on-line on an eight-channel chart recorder (Nyhon Kohden, Tokyo, Japan) and continuously registered and displayed on a Pentium II Dell computer using Labview software (National Instruments, Austin, Texas). Hemodynamic parameters were automatically registered in 60-s intervals.

Continuous data are presented as the mean value  $\pm$  SD. Direct comparisons with the control group were analyzed with the Student *t* test (Statistica, Tulsa, Oklahoma). Data on oxygen metabolism were analyzed with analysis of variance with repeated measures for time (Statistica). In case of a significant difference ( $p < 0.05$ ) between groups, the Newman-Keuls test was used for post-hoc testing. This test corrects for multiple testing.

## RESULTS

**Hemodynamic changes.** The hemodynamic evolution during ischemia and reperfusion is summarized in Table 1. Based on the relative small area of ischemia, the general hemodynamic effect of coronary occlusion was mild. There was a slight decrease in cardiac output and mean BP and an increase in filling pressure. None of these changes are significant.

The pump produced  $4.1 \pm 0.4$  l/min at the maximal rotational speed. Initiation of the pump resulted in unloading, as indicated by a significant decrease in LV end-diastolic pressure, left atrial pressure, and first derivative of

**Table 1.** Hemodynamic Evolution During Ischemia and Reperfusion

|                    | Heart Rate<br>(beats/min) | Cardiac Output<br>(l/min) | Pump Flow<br>(l/min) | Mean ABP<br>(mm Hg) | LVEDP<br>(mm Hg) | dP/dt <sub>max</sub><br>(mm Hg/s) | dP/dt <sub>min</sub><br>(-mm Hg/s) | LAP<br>(mm Hg) |
|--------------------|---------------------------|---------------------------|----------------------|---------------------|------------------|-----------------------------------|------------------------------------|----------------|
| Baseline           |                           |                           |                      |                     |                  |                                   |                                    |                |
| Group 1            | 91 ± 9                    | 4.7 ± 0.6                 | —                    | 78 ± 8              | 10.1 ± 1.1       | 1,624 ± 203                       | 1,773 ± 165                        | 9.1 ± 0.5      |
| Group 2            | 93 ± 4                    | 4.7 ± 0.8                 | —                    | 78 ± 4              | 11.1 ± 1.8       | 1,559 ± 163                       | 1,769 ± 78                         | 9.9 ± 0.9      |
| Group 3            | 89 ± 9                    | 4.7 ± 0.7                 | —                    | 78 ± 5              | 10.4 ± 1.3       | 1,602 ± 161                       | 1,784 ± 265                        | 10 ± 2.1       |
| Group 4            | 91 ± 9                    | 4.4 ± 0.4                 | —                    | 76 ± 2              | 9.3 ± 1.0        | 1,592 ± 262                       | 1,935 ± 222                        | 8.4 ± 0.8      |
| During ischemia    |                           |                           |                      |                     |                  |                                   |                                    |                |
| Group 1            | 90 ± 6                    | 4.5 ± 0.7                 | —                    | 73 ± 6              | 11.6 ± 1.2       | 1,422 ± 115                       | 1,541 ± 180                        | 10.5 ± 0.7     |
| Group 2            | 93 ± 2                    | 4.6 ± 0.6                 | 4.1 ± 0.4            | 83 ± 4*             | 7.1 ± 1.7*       | 1,032 ± 153*                      | 1,192 ± 218*                       | 6.3 ± 2.0*     |
| Group 3            | 91 ± 10                   | 4.5 ± 0.6                 | —                    | 74 ± 5              | 11.2 ± 1.0       | 1,507 ± 122                       | 1,507 ± 227                        | 10.7 ± 1.8     |
| Group 4            | 90 ± 8                    | 4.3 ± 0.3                 | —                    | 73 ± 3              | 10.9 ± 1.9       | 1,436 ± 164                       | 1,568 ± 140                        | 10.1 ± 2.0     |
| During reperfusion |                           |                           |                      |                     |                  |                                   |                                    |                |
| Group 1            | 93 ± 10                   | 4.1 ± 0.5                 | —                    | 66 ± 7              | 11 ± 1.7         | 1,264 ± 137                       | 1,447 ± 293                        | 10 ± 1.4       |
| Group 2            | 94 ± 5                    | 4.4 ± 0.5                 | 4.1 ± 0.4            | 77 ± 4*             | 7.3 ± 1.4*       | 1,005 ± 189*                      | 1,079 ± 122*                       | 6.4 ± 1.5*     |
| Group 3            | 91 ± 6                    | 4.5 ± 0.4                 | 4.1 ± 0.4            | 78 ± 3*             | 7.2 ± 0.7*       | 1,023 ± 86*                       | 1,100 ± 122*                       | 6.8 ± 1.0*     |
| Group 4            | 92 ± 5                    | 4.3 ± 0.3                 | 2.4 ± 0.1            | 74 ± 2*             | 8.7 ± 1.4        | 1,201 ± 111                       | 1,287 ± 132                        | 7.9 ± 1.4      |

\*Significant difference compared with the control group (Student *t* test). Data are presented as the mean value ± SD.

ABP = arterial blood pressure; LAP = left atrial pressure; LVEDP = left ventricular end-diastolic pressure; dP/dt = first derivative of left ventricular pressure; Group 1 = no support; Group 2 = support during ischemia and reperfusion; Group 3 = support during reperfusion; Group 4 = partial support during reperfusion.

LV pressure. In addition, the diastolic BP was significantly increased, leading to an increase in mean perfusion pressure (from 78 ± 4 to 83 ± 4 mm Hg).

Support with reduced pump performance (group 4) led to a significant increase in mean BP but did not decrease the preload significantly.

**Myocardial metabolism.** Myocardial oxygen consumption was significantly influenced during the experiment (Fig. 2). The changes are significant in time and for the different groups in the evolution over time ( $p < 0.000001$ ). At reperfusion, myocardial oxygen consumption increased slightly.

The animals assisted with the pump showed an immediate and significant reduction in oxygen consumption. The degree of reduction was similar during ischemia and reperfusion. The reduction was more explicit when the pump was used at full performance. The effect of partial support (group 4) still resulted in a significant reduction in myocardial oxygen consumption ( $p = 0.000016$ ).

General myocardial metabolism is well indicated by the LER (Fig. 2). The LER changed significantly during the experiment. These changes are significant in time and in relation to the support group ( $p = 0.003$ ). However, the difference is only significant for the fully supported group during ischemia. The LER in the supported groups during reperfusion was not significantly increased, as compared with the control group.

**Myocardial blood flow.** Myocardial blood flow, expressed as ml/min per g, was measured in the area of coronary occlusion as well in the contralateral area. Flows are shown for the subendocardial and subepicardial regions (Fig. 3). There was no difference in myocardial blood flow at baseline or during ischemia. There was practically no flow in the occluded area during ischemia, indicating the absence of collateral blood flow. At reperfusion, the flow was significantly reduced in groups 1, 3, and 4. In group 2, myocardial blood flow was normal during reperfusion.

There were no changes in myocardial blood flow in the control areas throughout the experiment.

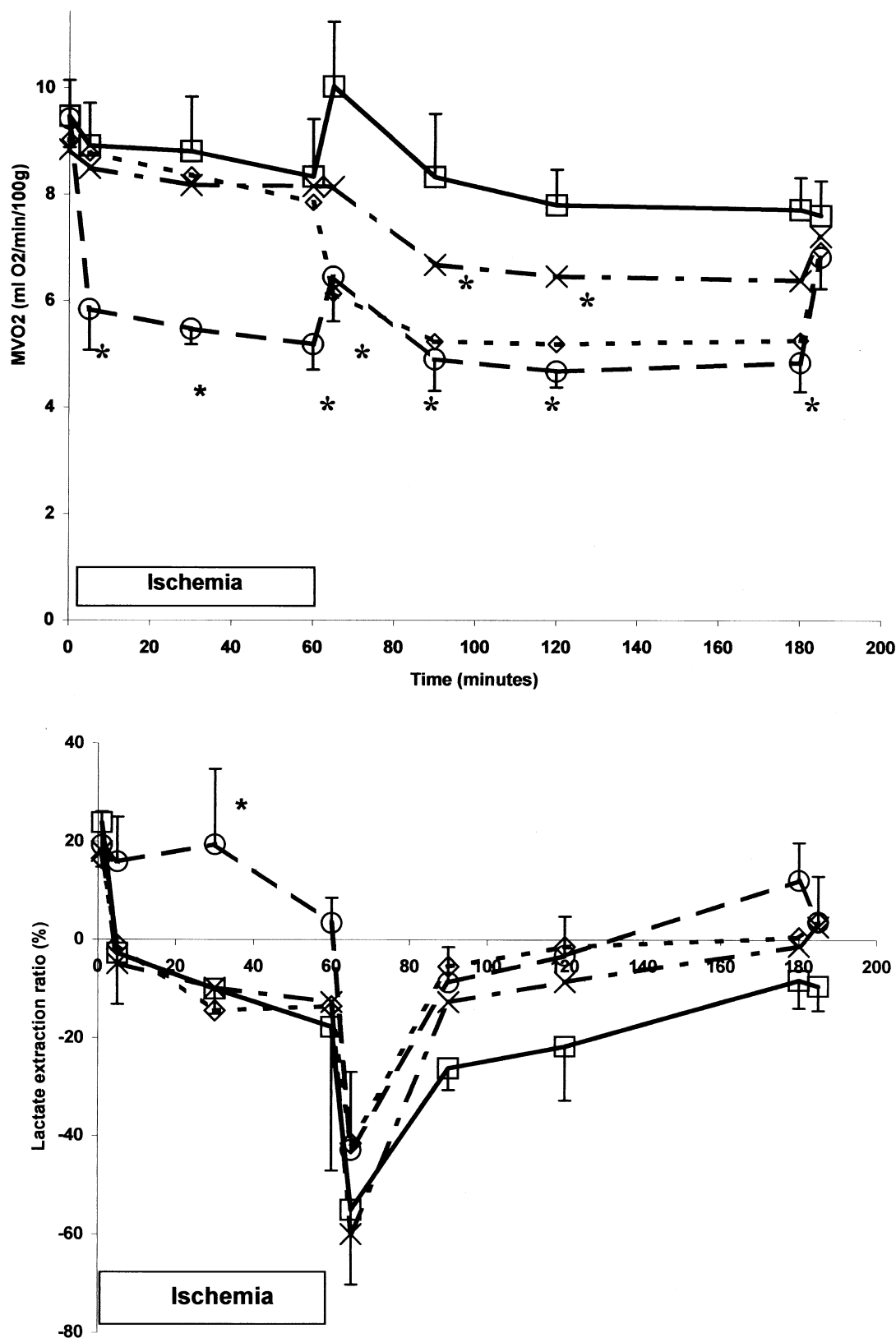
**Infarct size.** Myocardial infarct size is shown in Figure 4. The area at risk was small (15% of LV mass) and constant among all groups. There was a significant reduction in infarct size in the supported groups. The group supported throughout ischemia as well as reperfusion showed the most explicit reduction in infarct size (control:  $67.2 \pm 4.6\%$ ; support group:  $18.1 \pm 10\%$ ;  $p = 0.00001$ ). Both groups 3 and 4 showed a significant reduction in infarct size, as compared with the control group.

To assess the relationship between oxygen consumption and infarct size, independent of any intervention, we analyzed this relationship for the total group of tested animals (Fig. 5). The relationship is plotted for oxygen consumption during ischemia and for oxygen consumption during reperfusion. There is a strong correlation between infarct size and myocardial oxygen consumption during reperfusion, regardless of the animals' treatment ( $r = 0.9$ ).

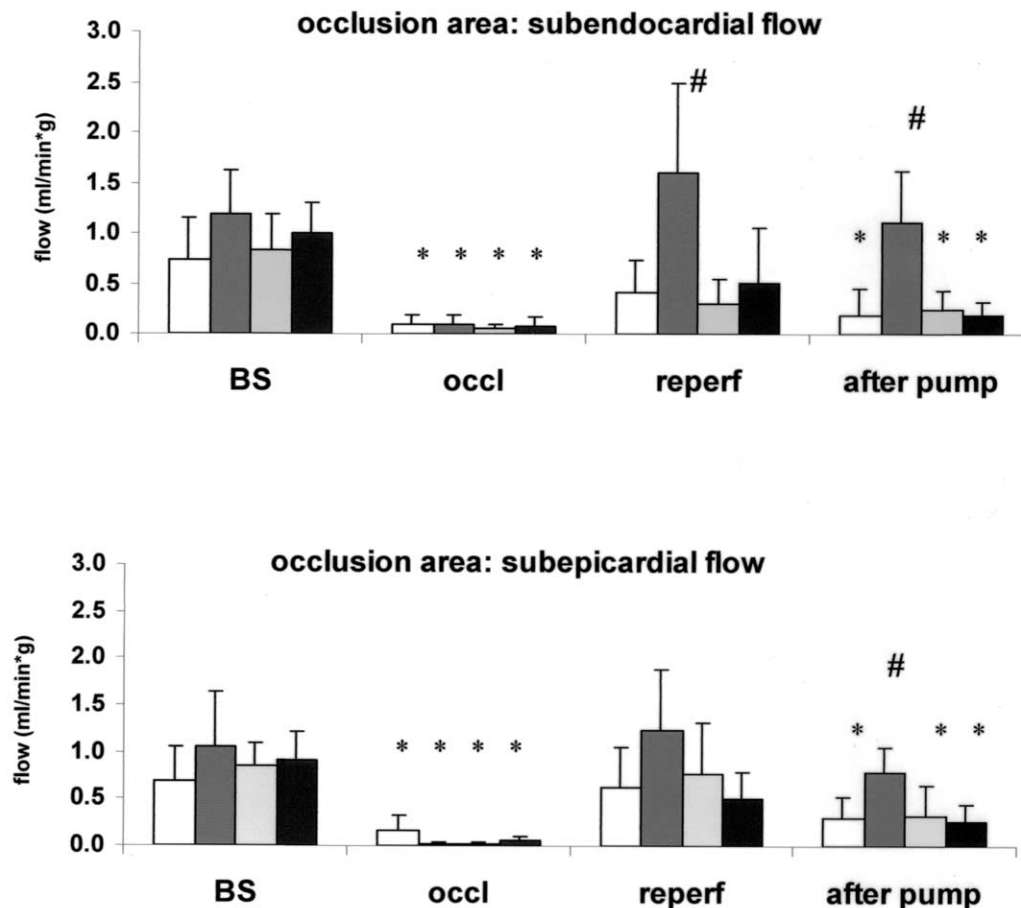
## DISCUSSION

In the management of acute MI, the primary focus has been to achieve early reperfusion. This intervention can reduce infarct size considerably, but the time restraints remain very important (22,23). When reperfusion is delayed, infarct size is significant. Several groups have shown beneficial effects of mechanical unloading during acute MI (24–28). Complete unloading using cardiopulmonary bypass, LV venting, and cardioplegia before reperfusion led to a 77% reduction of infarct size (24). This technique is not applicable as a primary approach for MI.

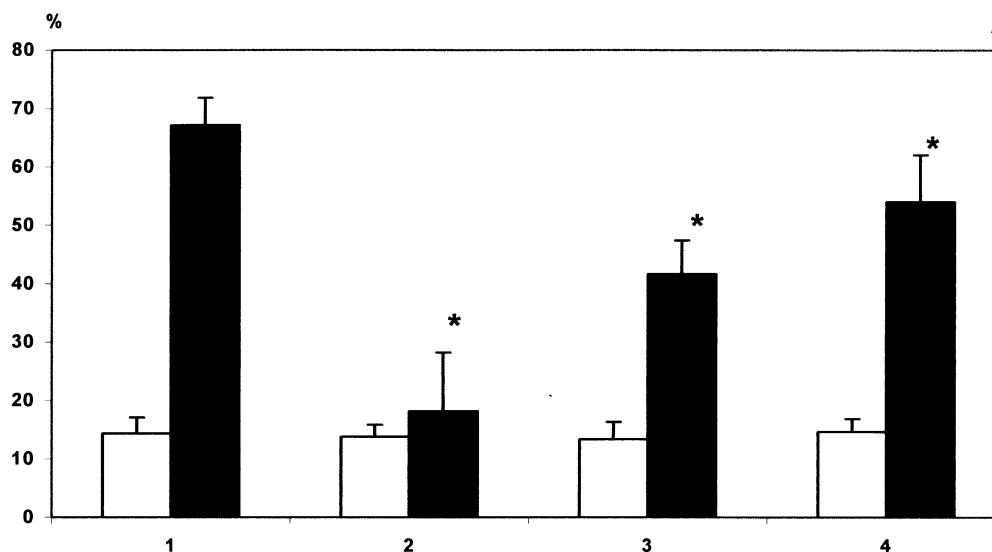
A more practical approach is the use of counterpulsation. Diastolic augmentation by intra-aortic balloon pumping has been shown to increase myocardial blood flow and myocardial oxygen supply (29). Some series have indicated that this increased myocardial blood flow leads to significant reduc-



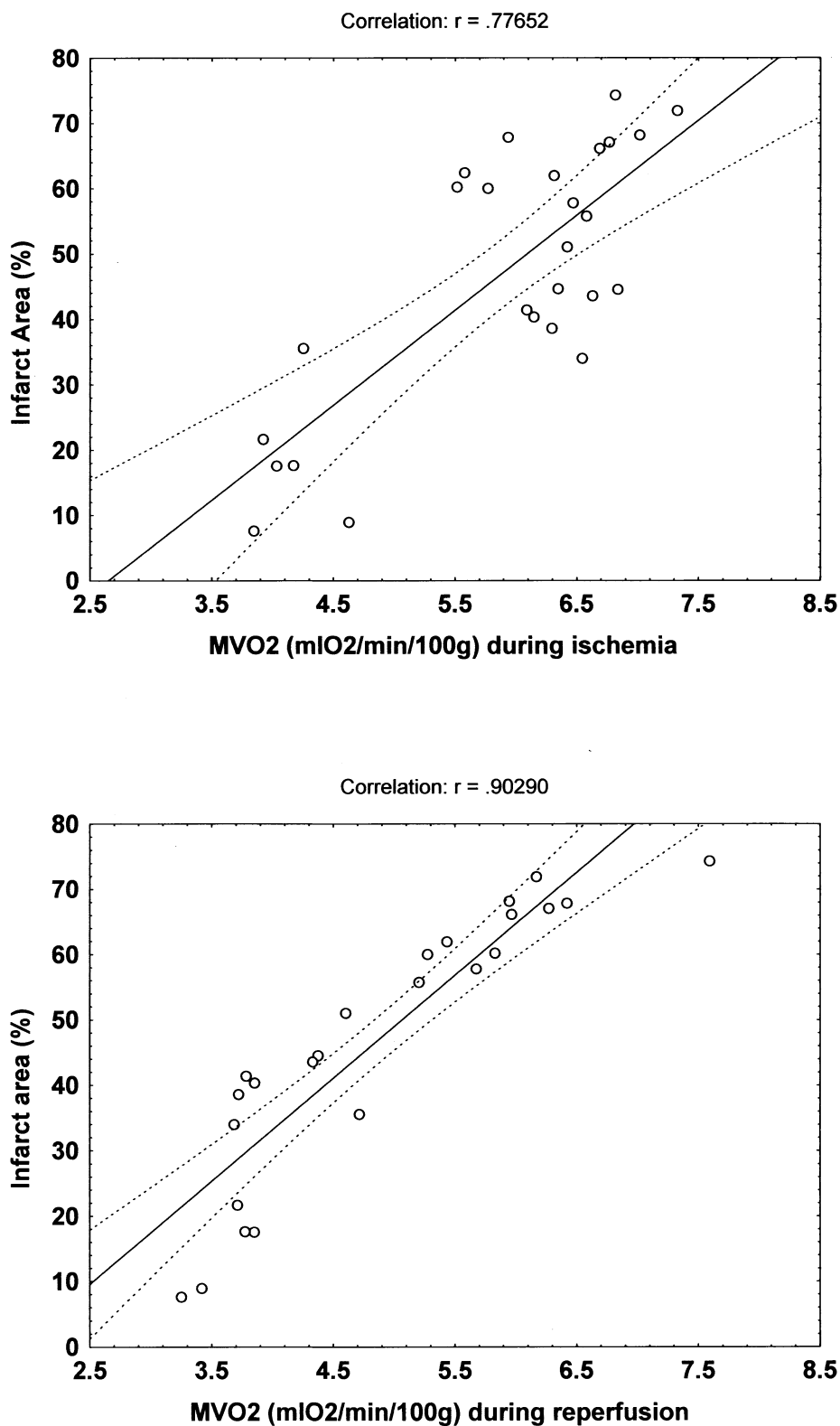
**Figure 2.** Myocardial metabolism during ischemia and reperfusion for the four different groups: control group (squares), fully supported group (circles), group supported during reperfusion only (diamonds), and group with partial support during reperfusion (×). \*Significant difference (analysis of variance with Newman-Keuls post-hoc testing;  $p < 0.05$ ) compared with the control group. Mechanical support influences myocardial oxygen consumption (MVO<sub>2</sub>) (upper panel). There was a significant reduction of oxygen consumption in all supported groups at all supported times. The lactate extraction ratio (LER) (lower panel) was significantly reduced during ischemia in all groups, except for the fully supported group. At reperfusion, the LER increased again, but the differences are not significant.



**Figure 3.** Myocardial blood flow in the subendocardial (upper panel) and subepicardial (lower panel) regions of the occluded area for the different groups (control group represented by open bars; fully supported group = darker shaded bars; group supported in reperfusion only = lighter shaded bars; and group with partial support during reperfusion = solid bars). During occlusion, there was almost no flow in either of the groups. At reperfusion, the fully supported group was the only group to show normal myocardial perfusion. BS = baseline; occl = during coronary occlusion; reper = reperfusion. \*Significant difference (Student *t* test) compared with the baseline value. #Significant difference (Student *t* test) compared with the control group.



**Figure 4.** Myocardial infarct sizes of the four different groups: 1 = control group; 2 = full support during ischemia and reperfusion; 3 = full support during reperfusion only; 4 = partial support during reperfusion only. The open bars indicate the area at risk; solid bars indicate infarct size. The intervals indicate the standard deviation of the mean value. \*Significant difference (Student *t* test) compared with the control group.



**Figure 5.** Correlations between myocardial oxygen consumption ( $MVO_2$ ) during ischemia (**upper panel**) and during reperfusion (**lower panel**) and the final infarct size of each animal. Infarct size correlated better with  $MVO_2$  during reperfusion. The intervals indicate the 95% confidence intervals. **Solid lines and circles** represent the regression with 95% confidence limits.

tions of infarct size in experiments of acute MI in canine models (30,31). However, studies performed in other than canine models have showed that intra-aortic balloon pumping does not lead to a significant reduction of infarct size (32,33). Studies with the Hemopump (Medtronic, Minneapolis, Minnesota) showed that support with a miniaturized transvalvular LV assist device results in increased myocardial perfusion in ischemic areas (34,35). Unloading the heart with the Hemopump resulted in a reduction of infarct size from 62.6% in the control group to 21.7% in the supported group in a canine infarction model (28).

Most of the studies investigating the role of mechanical support during MI were performed in dogs and show increased myocardial perfusion. It is well established that the collateral circulation is a major determinant of infarct size in dogs (36). However, the degree of collateral circulation in patients varies enormously and most often is not predictable. We studied the effect of unloading in the ovine heart, as it has no preexisting coronary collateral vessels, its infarctions have sharply defined borders, and coronary anatomy varies little between sheep (37–39). In addition, we opted for a small myocardial area at risk to avoid the confounding effect of cardiogenic shock and to study the unloading capacities of the device.

As a consequence, the hemodynamic effects of ischemia are very limited, allowing a stable experimental protocol. The observed hemodynamic effects of the microaxial pump are therefore predominantly unloading and an increase of the diastolic (and consequently the mean) BP. This unloading resulted in a significant reduction of infarct size, as shown by TTC staining. The reduction of infarct size is significant for all groups supported by the microaxial pump. The effect is most dramatic for the group supported during ischemia and reperfusion. The measured infarct sizes in the different groups are in accordance with the significant reduction in subendocardial blood flow during reperfusion in these animals—described as the “no-reflow phenomenon” (40). In contrast, the animals supported fully throughout the experiment with the microaxial blood pump showed normal subendocardial perfusion during reperfusion.

The mechanism of the observed salvage of myocardial tissue can be double: myocardial perfusion is increased in the area at risk through collateral circulation and the metabolic needs are reduced. During support, the mean perfusion pressure and especially the diastolic perfusion pressure were significantly increased in all groups. Secondly, the end-diastolic LV pressure was lower in all groups supported with the microaxial pump. However, with total coronary occlusion, blood flow in the ischemic area should be provided by preexisting collateral circulation, and this is known to be almost absent in healthy sheep. In addition, we measured no increase in myocardial perfusion in the ischemic area of the supported animals.

The observed reduction in myocardial oxygen consumption is significant and directly related to the degree of mechanical support. As a consequence, the reduction in

infarct size correlates with the reduction in oxygen consumption. In addition, the LER in the supported group was almost normal during ischemia. Therefore, the reduction in metabolic need is the major mechanism of the observed reduction in infarct size in this series.

An important parameter of infarct size is the size of the area at risk (36). Small areas have relatively more collateral flow and are more resistant to ischemia. However, the mechanism of myocardial salvage, as shown in this study, is based on a reduction of myocardial oxygen consumption and not on an increase in collateral flow. Therefore, we expect that the shown benefits are present in all infarcts, irrespective of their size. The hemodynamic effect of this pump (increased diastolic BP and decreased filling pressure) suggests that myocardial perfusion will also benefit patients with existing collateral circulation. Previous studies on myocardial perfusion in the ovine model with stenotic (not occluded) vessels showed that the microaxial pump increases myocardial flow in ischemic areas in a more efficient way than balloon counterpulsation (35).

Clearly, the beneficial effect of the pump depends also on the degree of support. We specifically tested the effect of the so-called “partial support,” as it is technically possible to provide this flow with the percutaneous device (outer diameter 4 mm). The larger pump has an outer diameter of 6.4 mm and requires a surgical cut-down of the femoral artery to allow safe introduction. Although a cut-down is acceptable in terms of invasiveness, it influences the availability and practicality of the approach.

The clinical application of this pump is dual: the pump supports the failing circulation (treatment of shock patients), and early unloading results in a reduction of infarct size.

Although animals supported during reperfusion had a significant reduction of infarct size, our data indicate that myocardial salvage is better when the heart is supported early (during ischemia). In the clinical setting of acute MI, reperfusion is often achieved late (41). Salvage of myocytes after MI is believed to be possible in the first 6 h after the onset of ischemia.

Prolonged unloading with administration of nitrates proved beneficial for ventricular function, even after late reperfusion (42,43). Technically, the pump can be used safely for seven days. However, the benefit of prolonged mechanical unloading is undone by the inevitable immobilization of the patient, instrumented with a pump through the femoral artery. Therefore, the major benefit of myocardial unloading with the micropump in acute MI is to be found in the first hours of reperfusion or, if at all possible, during ischemia.

**Conclusions.** Support with the Impella microaxial blood pump reduces the infarct size in an animal model. The mechanism of this effect is based on a reduction in metabolic need. The effect of this unloading is stronger when applied early (during ischemia) and is related to the degree of unloading.



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